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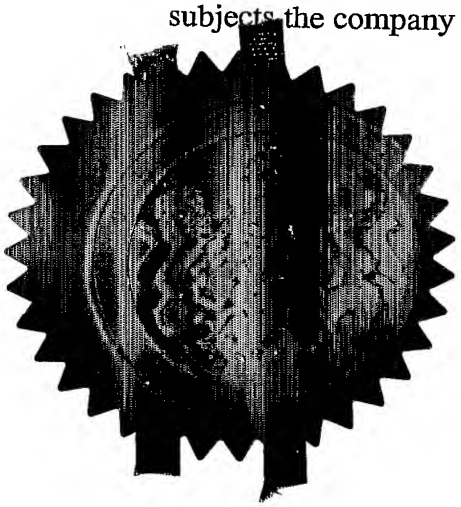

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REP07697GB

2. Patent application number
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0404953.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
Little Chesterford
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Patents ADP number *(if you know it)*

08306198001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Pro-drugs

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
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Patents ADP number *(if you know it)*

745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	16
Claim(s)	4
Abstract	
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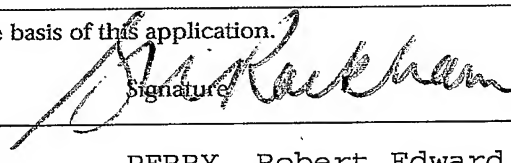
10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature  Date 4 March 2004

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PERRY, Robert Edward
020 7377 1377

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PRO-DRUGS

Field of the Invention

The present invention relates to novel dihydroxyanthraquinone carboxylic acid derivatives with improved physicochemical properties and that inhibit T-cell proliferation, processes for their preparation and their utility in the treatment of disease.

Background to the Invention

T-lymphocytes are known to play a central role in the pathogenesis of many inflammatory and autoimmune diseases. The activation of T-cells by antigen presenting cells is the primary event in the initiation of the inflammatory process, which subsequently leads to the activation of other inflammatory cells and in turn the release of pro-inflammatory cytokines, chemotactic agents and matrix degrading enzymes. In the case of rheumatoid arthritis the recruitment and activation of synovial macrophages by CD4+ T-cells leads to the secretion of high levels of TNFα, IL-1β and other pro-inflammatory cytokines. These cytokines induce the expression of cartilage-degrading enzymes (i.e. matrix metalloproteinases such as collagenase) and activate osteoclasts. This cascade of events results ultimately in the degradation of articular cartilage and the underlying bone (P. Isomaki and J. Punnonen, *Ann. Med.,* 1997, **29**, 499-507).

Multiple sclerosis is a chronic demyelinating inflammatory disease of the central nervous system. T-cell proliferation leads to release of the pro-inflammatory cytokines (primarily IL-2 and IFN-γ) and the recruitment of leucocytes (including macrophages) which orchestrate the inflammatory response (via the release of TNFα, IL-1β and other pro-inflammatory cytokines) in regions of the myelin sheath leading to demyelination. This process slows the transmission of nerve impulses leading ultimately to oligodendrocyte destruction and damage to the axonal membrane (E. Prat, *et al*, *J. Rehabil. Res. Dev.*, 2002, **39 (2)**, 187-199).

In chronic obstructive pulmonary disease (COPD) activation of neutrophils and macrophages by proliferating CD8+ T-cells leads to the release of pro-inflammatory cytokines and elastin degrading enzymes [such as neutrophil elastase (HNE) and metalloelastase (MMP-12)] which cause a chronic and progressive degradation of lung tissues and ultimately reduction in respiratory function (M. G. Cosio, *et al, Chest*, 2002, **121 (5)**, 160S-165S and P. Barnes, *Trends in Pharmaceutical Sciences*, 1998, **19**, 415-423).

Crohn's disease and ulcerative colitis are chronic inflammatory diseases of the intestines collectively known as inflammatory bowel disease (IBD). It is likely that both these disorders are actually heterogeneous groups of diseases that have different causes, but share similar perpetuating stimuli and common pathways of tissue injury. Once again T-cells are central to the progression of this collection of diseases leading to the activation of immune, mesenchymal and epithelial cells, recruitment of circulating effector cells and ultimately gastrointestinal tissue damage. IL-1β and TNFα are key immunoregulatory cytokines that amplify the immune response by further activating a cascade of immune cells producing other pro-inflammatory cytokines, arachidonic acid metabolites and proteases (A. Kappeler, *et al*, *Histol. Histopathol.*, 2000, **15 (1)**, 167-172).

In psoriasis the presentation of antigen by Langerhan's cells to CD4+ T-cells leads to the synthesis of cytokines which stimulate keratinocyte proliferation and the expression of adhesion molecules by endothelial cells and keratinocytes. Keratinocytes in turn are stimulated to produce their own cytokines which can act in an autocrine and/or paracrine manner to maintain the psoriatic process (J.-P. Ortonne, *British Journal of Dermatology*, 1996, **135 (suppl. 49)**, 1-5).

There is a similarly strong rationale for the central involvement of T-cells in many other inflammatory diseases including, systemic lupus erythematosus (SLE) (M.J. Yellin, *et al*, *Curr. Rheumatol. Rep.*, 2000, 2

(1), 24-31) and asthma (L. Maddox, *et al, Annu. Rev. Med.*, 2002, **53**, 477-498) ; lupus nephritis (M. H. Foster, *et al, Smin. Nephrol.,* 1999, **19 (2)**, 173-181), glomerulonephritis (A. R. Kitching, *et al, Histol. Histopathol.*, 2000, **15 (3)**, 993-1003) and IgA nephropathy (J. Feehally, *et al, Ann. Med. Interne.*, 1999, **150 (2)**, 91-98); gingivitis (R. C. Page, *J. Clin. Periodontol.,* 1986, **13 (5)**, 345-359) and periodontal disease (A. Mathur, *et al, Crit. Rev. Oral Biol. Med.,* 1997, **8 (1)**, 76-89); atopic dermatitis (A. Cantani, *Eur. Rev. Med. Pharmacol. Sci.*, 2001, **5 (3)**, 95-117), scleroderma (C. Scaletti, *et al, Int. Arch. Allergy Immunol.*, 2001, **125 (3)**, 196-202) and graft vs host disease (GVHD) (B. R. Blazar, *et al, Immunol. Rev.,* 1997, **157**, 79-109). Thus inhibitors of T-cell proliferation are much sought after and will have utility in the treatment of the range of inflammatory and autoimmune diseases described in detail above.

Rhein (1,8-dihydroxyanthraquinone-3-carboxylic acid) is well characterised anti-inflammatory agent with recognised utility in a range of inflammatory diseases. While this agent has not been demonstrated to inhibit T-cell proliferation it is known to inhibit the production of pro-inflammatory cytokines (IL-1β and TNFα) in human osteoarthritic synovium and chondrocytes (J. Martel-Pelletier *et al*, *Journal of Rheumatology*, 1998, **25 (4)**, 753-762) and to inhibit cytokine gene expression in a model of lupus nephritis (S. Lemay *et al*, Kidney International, 1996, **50 (1)**, 85-93). In common with the tetracyclines, rhein and it's pro-drug diacerein have been shown to down-regulate the production of pro-matrix metalloproteinases (pro-MMPs -1, -3, -9 and -13) while upregulating the production of tissue inhibitor of metalloproteinases -1 (TIMP-1) from rabbit articular chondrocytes (T. Tamura *et al*, *Osteoarthritis and Cartilage*, 2001, **9 (3),** 257-263). This potential combination of disease-modifying and anti-inflammatory activities has resulted in the use of rhein in arthritis and multiple sclerosis (US 4346103, C. A. Friedman, 1982) and in diabetic nephropathy (EP 0 990 441 A1, Nanjing General Hospital, April 2000),

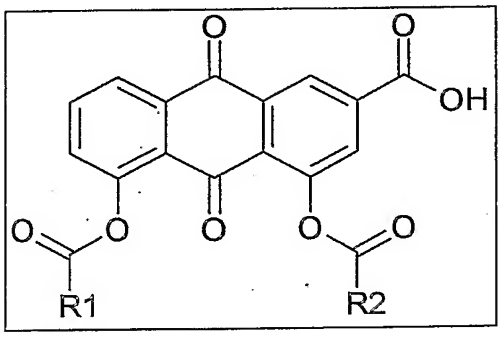
diseases where over-production of IL-1β is particularly implicated. The more widespread use of rhein has been somewhat limited by its rather poor physicochemical properties. This issue is not addressed completely with the well characterised pro-drug diacerein where utility in the clinical setting is again limited by poor physicochemical properties (P. Nicolas *et al*, *Clin. Pharmacokinet.*, 1998, **35 (5)**, 347-359).

The present invention is related to our observation that simple ester derivatives of rhein are capable of inhibiting cytokine production and T-cell proliferation in assays where rhein itself and other simple derivatives fail to produce a response. It is likely that these agents will be of clinical utility in the wide range of inflammatory and autoimmune diseases described above, due to their improved physical properties over the parent compound.

Summary of the Invention

The invention encompasses novel dihydroxyanthraquinone carboxylic acid compounds of formula (**1**) which are useful as inhibitors of cytokine production and T-cell proliferation, and are therefore of utility in the treatment of T-cell mediated diseases including those described above.

In the first aspect of the invention there is provided a compound of general formula (**1**):



(1)

Wherein:

R_1 and R_2 may be the same or different taken from C_{1-4} alkyl substituted with R_3, and can be a four to seven membered ring which can be optionally substituted with R_8 and can contain one or more additional heteroatoms taken from the list O, S(O)n, NR_{10} ; n is an integer 0-2.

R_3 is CF_3, OR_4, NR_5R_6 or $S(O)nR_7$; n is an integer 0-2

R_4, R_5, R_6, may be the same or different from H, C_{1-4} alkyl optionally substituted with R_3. R_5 and R_6 may form a C_{4-6} heterocycloalkyl ring containing one or more heteroatoms taken from O, NR_9, S(O)n; n is an integer 0-2.

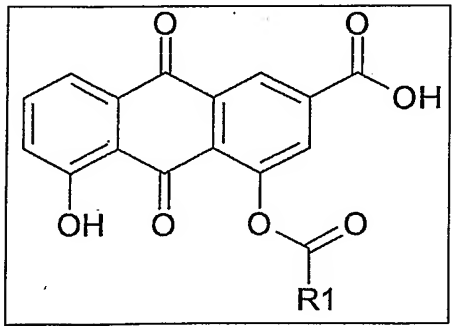
R_7 may be C_{1-4} alkyl

R_8 may be as R_3 ,or C_{1-4} alkyl optionally substituted with R_3, or halogen

R_9 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof.

In the second aspect of the invention there is provided a compound of general formula (**2**):



(2)

Wherein:

R_1 may be C_{1-4} alkyl substituted with R_2. or a four to seven membered ring which can be optionally substituted with R_7 and can

contain one or more additional heteroatoms taken from the list O, S(O)n, NR_9 ; n is an integer 0-2.

R_2 may be CF_3, OR_3, NR_4R_5 or $S(O)_nR_6$; n is an integer 0-2

R_3, R_4, R_5, may be the same or different from H, C_{1-4} alkyl, optionally substituted with R_2. R_4 and R_5 may form a C_{4-6} heterocycloalkyl ring, containing one or more heteroatoms taken from O, NR_8 , S(O)n; n is an integer 0-2.

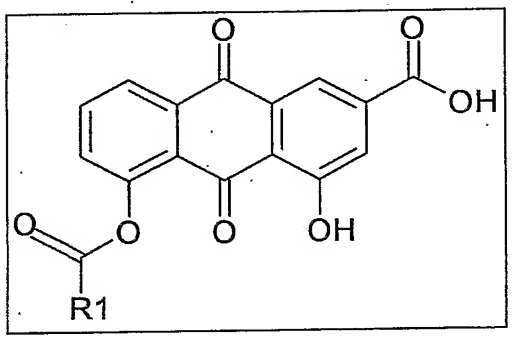
R_6 may be C_{1-4} alkyl

R_7 may be as R_2, C_{1-4} alkyl optionally substituted with R_2, or halogen

R_8 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof.

In the third aspect of the invention there is provided a compound of general formula (**3**):



(3)

Wherein:

R_1 may be C_{1-4} alkyl substituted with R_2. or a four to seven membered ring which can be optionally substituted with R_7 and can contain one or more additional heteroatoms taken from the list O, S(O)n, NR_9 ; n is an integer 0-2

R_2 may be CF_3, OR_3, NR_4R_5 or $S(O)_nR_6$; n is an integer 0-2

R_3, R_4, R_5, may be the same or different from H, C_{1-4} alkyl, optionally substituted with R_2. R_4 and R_5 may form a C_{4-6}

heterocycloalkyl ring, containing one or more heteroatoms taken from O, NR_8 , S(O)n; n is an integer 0-2.

R_6 may be C_{1-4} alkyl

R_7 may be as R_2, C_{1-4} alkyl optionally substituted with R_2, or halogen

R_8 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (**1**), **(2)** and **(3)** can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

The term "C_{1-4} alkyl" refers to a straight or branched chain alkyl moiety having from one to four carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl and the like.

The term "C_{4-6} heterocycloalkyl" refers to a saturated heterocyclic moiety having from three to six carbon atoms and one or more heteroatom from the group N, O, S and includes for example azetidinyl, oxetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

Salts of compounds of formula (**1**), **(2)** and **(3)** include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts

such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

A carboxyl group can be protected in the form of a readily cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester.

Compounds of the general formula **(1)**, **(2)** and **(3)** may be prepared by any suitable method known in the art and/or by the following processes, which itself forms part of the invention.

According to another aspect of the invention, there is provided a process for preparing a compound of general formula **(1)**, **(2)** and **(3)** as defined above. It will be appreciated that where a particular stereoisomer of formula **(1)**, **(2)** or **(3)** is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers maybe resolved from mixtures using conventional separation techniques (eg. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R_1, R_2, R_3, R_4, R_5, R_6 R_7, R_8, and R_9 are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details see "Protective Groups in Organic Synthesis", Wiley Interscience, T W Greene, PGM Wuts.

The process required for preparing compounds of general formula **(1)** comprises of:

Conversion of the activated ester in the presence of base, (such as Diacerein to Rhein), followed by reaction with the required acid chloride. Diacerein and the corresponding acid chlorides are either

commercially available or readily obtained from commercially available materials by people who are skilled in the art of synthetic organic chemistry.

The process required for preparing compounds of general formula **(2)** and **(3)** will be similar to that described for **(1),** but will necessitate the additional steps of selectively protecting one hydroxyl group prior to the reaction with the acid chloride, and this will have to be followed by a deprotection step to reveal the target compound.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds of formula (**1**), **(2)** and **(3)** according to the invention exhibit *in vitro* inhibiting activities with respect to T-cell proliferation. Compounds according to the invention also exhibit *in vitro* inhibition of pro-inflammatory cytokine release. The activity of the compounds may be determined by use of the appropriate cellular assay, for example as described in Example A herein after.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to T-cell proliferation as previously described, and more specifically, a method of treatment involving the administration of the T-cell proliferation inhibitors of formula (**1**), **(2)** or **(3)** as the active constituents.

Accordingly, the compounds of formula (**1**), **(2)** and **(3)** can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, psoriasis, systemic lupus erythromatosis (SLE), multiple sclerosis, chronic obstructive pulmonary disease (COPD) and

inflammatory bowel disease including ulcerative colitis and Crohn's disease.

As mentioned above, compounds of formula **(1)**, **(2)** and **(3)** are useful in human or veterinary medicine since they are active as inhibitors of T-cell proliferation. Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment of prophylaxis) of disease or conditions mediated by T-cells in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound of formula **(1)**, **(2)** or **(3)** above, or a pharmaceutically acceptable salt thereof; and

a compound of formula **(1)**, **(2)** or **(3)** for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by T-cells; and

the use of a compound of formula **(1)**, **(2)** or **(3)** in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by T-cells.

The disease or conditions referred to above include inflammatory and autoimmune diseases such as rheumatoid arthritis, osteoarthritis, osteoporosis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis, graft versus host reactions, psoriasis, scleroderma, atopic dermatitis, asthma, systemic lupus erythematosus (SLE), nephropathy and chronic obstructive pulmonary disease (COPD).

For the treatment of rheumatoid arthritis, multiple sclerosis, and in other diseases and indications resulting from the over-activity of T-cells such as those highlighted above, the compounds of formula **(1)**, **(2)** or **(3)** may be administered orally, topically, parenterally, by inhalation or nasal spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections,

intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyeryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108;4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft

gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and

suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occuring gums, for example gum acacia or gum tragacanth, naturally-occuring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example gycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (**1**), **(2)** and **(3)** may also be administered in the form of suppositories for rectal administration of the

drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (**1**), **(2)** and **(3)** are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 gms per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

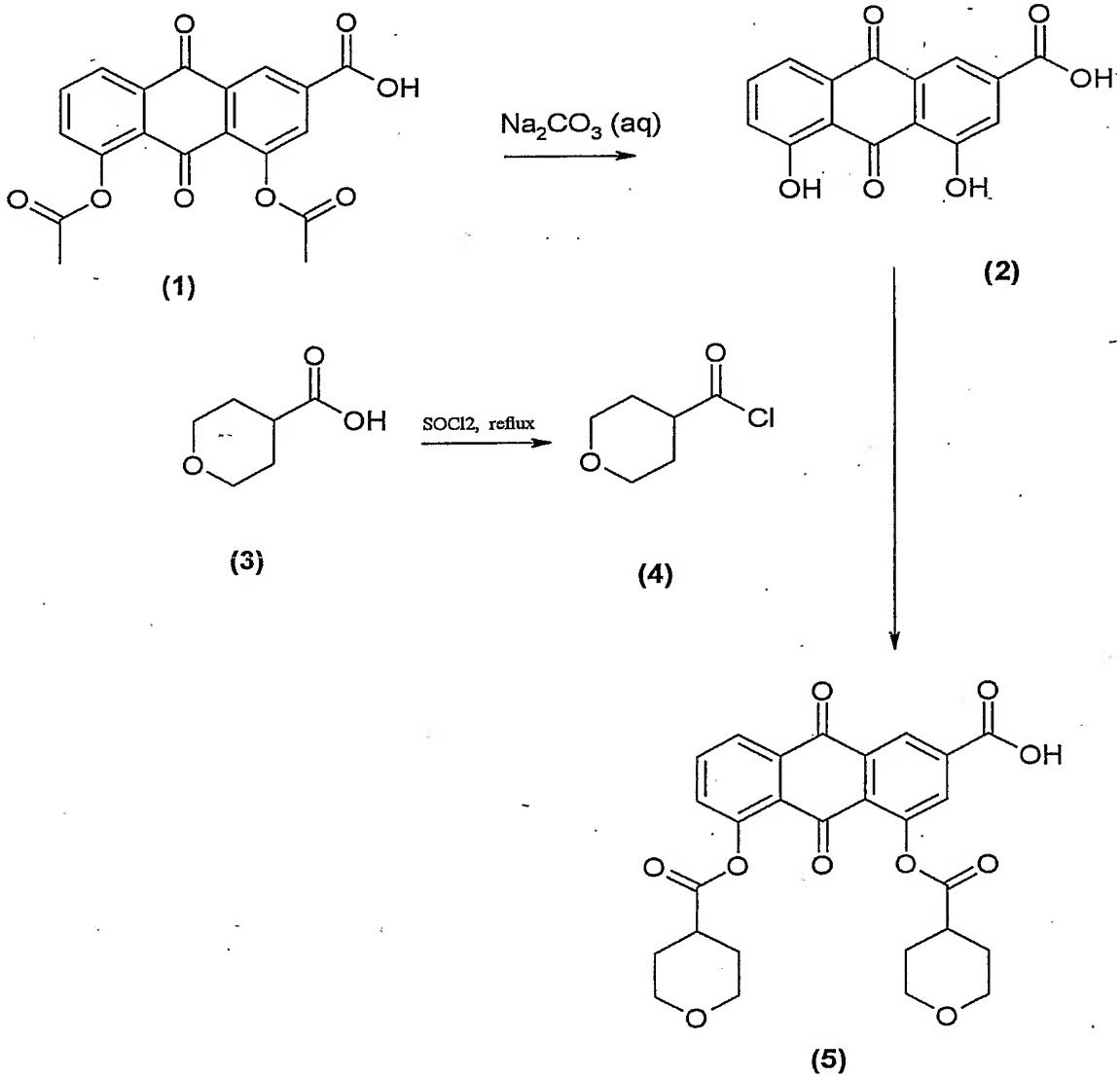
Examples

The invention is substantiated by the following list of examples:

Example 1

4,5-ditetrahydropyranoyloxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid

Scheme



Diacerein, **1**, (13 g) and aq. Na_2CO_3 (10% w/v. 400 mL) were charged to a 3-necked 1 L flask and stirred at room temperature overnight. The pH of the red solution was adjusted to pH 3 by adding 2M HCl, which resulted in a solid precipitating out of solution. The solid was filtered and dried in a vacuum oven overnight to give an orange solid (13.1 g). This was slurried in water (200 mL), filtered and dried in a vacuum oven to give 10.5 g, 104.6% of diol , **2**. ^{1}H NMR (DMSO-d_6) : 8.15 (1H, s), 7.60 (3H, m), 7.35 (1H, m).

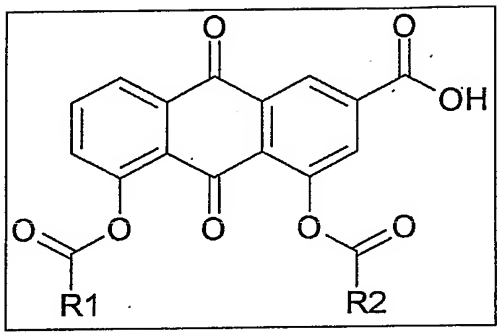
Tetrahydropyran-4-yl carboxylic acid, **3** (5.8 g) was charged to a 250 mL 3-necked flask, followed by thionyl chloride (116 mL), then stirred at reflux for 2.5 h. TLC of the reaction mixture after having been quenched in MeOH showed complete conversion of the starting material. After allowing the reaction mixture to cool to room temperature, thionyl chloride was then removed *in vacuo* to leave a yellow oil. This was diluted with DCM (30 mL) and transferred to another flask, then the DCM removed *in vacuo* to leave acid chloride **4** as a yellow oil (6.6 g, 100%). ^{1}H NMR (CDCl3) : 3.95 (2H, m), 3.35 (2H, m), 2.95 (1H, m), 1.65-2.1 (4H, m).

Diol **2** (3.6 g) was charged to a 250 mL 3-necked flask, followed by pyridine (115 mL) and 4Å MS (30 g), then the mixture was stirred for 1 h. Acid chloride **4** (6.4 g) was then added and the reaction mixture was left stirring overnight. More acid chloride **4** (0.2 g, 0.1 eq.) was added to facilitate further conversion, and the mixture stirred for 1.5 h. The reaction was quenched with 1M HCl (100 mL) and the pH decreased to 2 using 1M HCl (650 mL), and 4.5M HCl (250 mL), resulting in the formation of a yellow precipitate. The precipitate was filtered and partitioned between EtOAc (500ml) and 1M HCl (3 x 500ml). The organic phase was dried over $MgSO_4$ (90g), filtered and concentrated to give a sticky, yellow solid. This was triturated in Et_2O (20mL) and dried in a vacuum oven at 40 °C, overnight. The yield of THP pro drug Rhein **5** = 2.9 g, 44.9%.

^{1}H NMR (DMSO-d_6) : 8.65 (1H, s), 7.9-8.2 (3H, m), 7.65 (1H, m), 3.95 (4H, m), 3.3-3.5 (4H, m), 2.85 (2H, m), 1.6-2.2 (8H, m).

Claims

1. A compound of general formula (**1**):



(**1**)

Wherein:

R_1 and R_2 may be the same or different taken from C_{1-4} alkyl substituted with R_3, and can be a four to seven membered ring which can be optionally substituted with R_8 and can contain one or more additional heteroatoms taken from the list O, S(O)n, NR_{10} ; n is an integer 0-2.

R_3 is CF_3, OR_4, NR_5R_6 or $S(O)nR_7$; n is an integer 0-2

R_4, R_5, R_6, may be the same or different from H, C_{1-4} alkyl optionally substituted with R_3. R_5 and R_6 may form a C_{4-6} heterocycloalkyl ring containing one or more heteroatoms taken from O, NR_9, S(O)n ; n is an integer 0-2.

R_7 may be C_{1-4} alkyl

R_8 may be as R_3 ,or C_{1-4} alkyl optionally substituted with R_3, or halogen

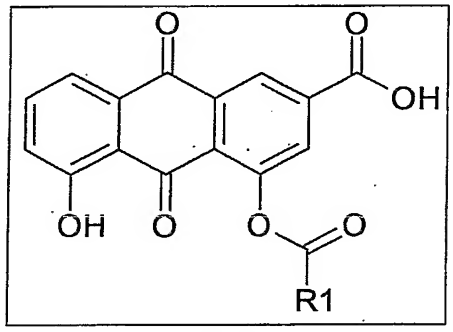
R_9 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof.

2. A compound of claim 1, selected from:

4,5-ditetrahydropyranoyloxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid

3. A compound of general formula **(2)**



(2)

Wherein:

R_1 may be C_{1-4} alkyl substituted with R_2 , or a four to seven membered ring which can be optionally substituted with R_7 and can contain one or more additional heteroatoms taken from the list O, S(O)n, NR_9 , n is an integer 0-2.

R_2 may be CF_3, OR_3, NR_4R_5 or $S(O)_nR_6$; n is an integer 0-2

R_3, R_4, R_5, may be the same or different from H, C_{1-4} alkyl, optionally substituted with R_2. R_4 and R_5 may form a C_{4-6} heterocycloalkyl ring, containing one or more heteroatoms taken from O, NR_8 , S(O)n ; n is an integer 0-2.

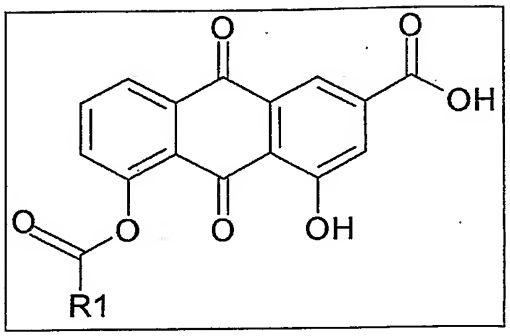
R_6 may be C_{1-4} alkyl

R_7 may be as R_2, C_{1-4} alkyl optionally substituted with R_2, or halogen

R_8 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof

4. A compound of general formula **(3).**



(3)

Wherein:

R_1 may be C_{1-4} alkyl substituted with R_2 or a four to seven membered ring which can be optionally substituted with R_7 and can contain one or more additional heteroatoms taken from the list O, S(O)n, NR_9; n is an integer 0-2.

R_2 may be CF_3, OR_3, NR_4R_5 or $S(O)_nR_6$; n is an integer 0-2

R_3, R_4, R_5, may be the same or different from H, C_{1-4} alkyl, optionally substituted with R_2. R_4 and R_5 may form a C_{4-6} heterocycloalkyl ring, containing one or more heteroatoms taken from O, NR_8, S(O)n ; n is an integer 0-2.

R_6 may be C_{1-4} alkyl

R_7 may be as R_2, C_{1-4} alkyl optionally substituted with R_2, or halogen

R_8 may be H or C_{1-4} alkyl

and the salts, solvates and hydrates thereof.

5. A compound of any preceding claim in the form of a single enantiomer or diastereoisomer or a mixture of such isomers.

6. A pharmaceutical composition for use in therapy, comprising of a compound of any of claims 1 to 5 and a pharmaceutically acceptable diluent or carrier.

7. Use of a compound of any of claims 1 to 5, for the manufacture of a human or veterinary medicament for the treatment or prevention of a

condition associated with T-cell proliferation or that is mediated by pro-inflammatory cytokines, particularly IL-1β or IL-18.

8. Use according to claim 7, wherein the condition is a chronic degenerative disease such as rheumatoid arthritis, osteoarthritis or osteoporosis.

9. Use according to claim 7, wherein the condition is a chronic demyelinating disease such as multiple sclerosis.

10. Use according to claim 7, wherein the condition is a respiratory disease such as asthma or chronic obstructive pulmonary disease (COPD).

11. Use according to claim 7, wherein the condition is an inflammatory bowel disease (IBD) such as ulcerative colitis or Crohn's disease.

12. Use according to claim 7, wherein the condition is a dermatological condition such as psoriasis, scleroderma or atopic dermatitis.

13. Use according to claim 7, wherein the condition is a dental disease such as periodontal disease or gingivitis.

14. Use according to claim 7, wherein the condition is diabetic nephropathy, lupus nephritis, IgA nephropathy or glomerulonephritis.

15. Use according to claim 7, wherein the condition is systemic lupus erythematosus (SLE).

16. Use according to claim 7, wherein the condition is graft vs host disease.